REMARKS

Claims 1-10, 13, and 14 are pending in this application. Applicants respectfully request reconsideration of the rejections and objections in view of the following remarks.

The specification is objected to and claims 1-10, 13, and 14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach one skilled in the art how to make and/or use the claimed invention. The Examiner argues that the specification fails to provide an enabling disclosure, stating that "[c]onstruction of claimed *Shigella* mutants requires knowledge of the nucleotide sequence of said genes, which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted." The Examiner continued by stating that "[d]ue to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation." Thus, the Examiner concluded "[t]he only means by which applicants can provide an enabling disclosure for the *Shigella* mutants is by depositing said mutants and limiting the claims to the deposited mutants."

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In essence, the Examiner is requiring that the claims be limited to only the deposited mutants.

Applicants respectfully traverse this rejection. Applicants respectfully disagree with the Examiner's objection to the specification under 35 U.S.C. § 112, first paragraph, as lacking enablement, and reassert the arguments set forth on pages 5-9 in the Response filed on December 20, 1996.

To establish a *prima facie* case of non-enablement, the Examiner must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one skilled in the art to make and use the claimed invention. The test for enablement is whether one skilled in the art could make or use the invention from the disclosures in the patent *coupled with information known in the art* without undue experimentation. (M.P.E.P. § 2164.01 (italics added).) Moreover, a patent need not teach, and preferably, may omit information well known in the art. (Id.)

The specification describes a method of making a modified strain of *Shigella*, wherein a gene necessary for (1) invasion, (2) spreading, and (3) production of toxins is permanently mutated, by either whole or partial deletions or permanent

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inactivation. This modified strain can be used to make *Shigella* vaccines.

Applicants submit that the DNA sequences of genes necessary for invasion and spreading of *Shigella*, for example, the iscA, virG, aerobactin, enterochelin, as well as the DNA sequences for the toxin-producing genes, were well known in the art at the time the application was filed. The Examiner acknowledges this point (Office Action 13, pg. 4, paragraph 3), but alleges that the evidence is not commensurate in scope with the claimed invention, which encompasses the inactivation of the genes responsible for invasion, spreading, and toxin production.

Applicants submit that, using the teachings of the instant specification and the knowledge generally available to the skilled artisan, one skilled in the art can perform routine experimentation to inactivate genes responsible for invasion, spreading, and toxin production. Applicants submit that one skilled in the art is enabled by the instant invention to permanently inactivate these genes.

The Examiner asserts that while it would appear that techniques are known in the art for inactivation, it is not routine to screen for positions within the DNA sequence of the gene so that it does not invade the cells, does not spread within

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infected cells, or does not produce toxins. Applicants submit herewith prior art references that clearly indicate the level of skill in the art prior to the filing of the instant application. Nassif et al. teaches assay procedures for *Shigella* mutations that affect invasion of cells (page 1694, second column, paragraph 3), toxin production (page 1694, second column, paragraph 4), and spread (page 1694, second column, paragraphs 5 and 6). Baudry et al. teaches assay procedures for *Shigella* mutations that affect invasion of cells (page 3405, paragraph 3) and toxin production (page 3405, paragraph 4). Maurelli et al. teaches assay procedures for *Shigella* mutations that affect invasion of cells (page 2820, second column, paragraph 4), toxin production (page 2821, first column, paragraph 1), and spread (page 2821, first column, paragraph 1). Applicants submit that these references contain the teachings necessary screening for *Shigella* genes involved the invasion of cells, spread within infected cells, and toxin production, which can be used in the practice of applicants' invention.

Furthermore, Applicants submit that once a gene is mutated and identified, one skilled in the art can clone the gene by methodology known to the skilled artisan. Maurelli et al. is provided as an example of the prior art indicating the cloning of

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a gene involved in virulence. Therefore, the skilled artisan can identify *Shigella* genes responsible for the invasion of cells, spread within infected cells, and toxin production using the teachings of the prior art.

Moreover, the specification teaches a method for inactivating genes. The specification teaches one skilled in the art that the exact position of the mutation is irrelevant, as long as the mutation causes permanent inactivation of such genes. (Specification, page 5, lines 8-36, page 6, lines 1-17.) The specification repeatedly requires that the genes necessary for invasion, spreading, and toxin-production, be "wholly or partly removed or permanently inactivated, preferably at least partly removed." (Specification, page 5, lines 26-28, lines 30-34, line 36, page 6, line 1). Therefore, one skilled in the art would not need to know which regions of the genes are responsible for activating or the number of nucleotides that must be deleted or inserted; the skilled artisan could use routine experimentation to remove the entire gene or mutate the gene in such a way as to eliminate protein production by the gene (e.g. frameshift mutation).

Although some experimentation may be necessary to carry out the claimed invention, the experimentation would not be undue,

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but merely routine. (M.P.E.P. § 2164.01.) Thus, as previously asserted in previous responses, "[i]n view of the extensive guidance provided by the specification and the background information which is present in the public domain, it is respectfully submitted that the Examiner has failed to establish that practicing the claimed invention would require undue experimentation" and therefore Applicants respectfully request that the objection to the specification and rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Although the Examiner requested that the plasmids SC502, SC503, and SC504 be deposited, Applicants respectfully assert that because the specification clearly enables one skilled in the art to make the claimed invention, a deposit of the strains is not required. (M.P.E.P. § 2402.02.)

The Examiner maintains provisional rejection of claims 13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 39 of copending application Serial No. 08/118,100. The Examiner argued that although the allegedly conflicting claims are not identical, the claims are not patentably distinct from each other because both are drawn to *Shigella* mutants, which have an inactivated gene encoding *Shiga*-toxin. Applicants respectfully request that the

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Examiner hold this provisional rejection in abeyance until allowable subject matter has been indicated in either of the applications.

Claims 13 and 14 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner argues that claims 13 and 14 do not contain antecedent basis for the term "genes". The phrasing suggested by the Examiner has been incorporated in the amended claims.

Conclusions

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. If the application is not allowed, applicants respectfully request that this amendment be entered for purposes of appeal because it eliminates issues from appeal.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this paper, such extension is hereby requested. If there are any fees due under 37 C.F.R.

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§ 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

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Dated: August 29, 1997

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